AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1.   (Currently Amended) A computer-based diagnostic method for estimating for a patient the treatment response of a disease caused by a pathogen to a drug, the method comprising:

a) inputting data related to the genotype exhibited by a disease causing pathogen to a computer apparatus;

b) determining, by the computer apparatus, the fold change resistance value of the pathogen infecting the patient;

c) determining, by the computer apparatus, a ~~comparing the fold change resistance value of the pathogen infecting the patient to a~~ clinical cut-off value which is the fold change resistance value at which a clinically relevant variation of clinical response is observed;

wherein the clinical cut-off value is established by modeling the clinical response of a population of patients treated with the drug to the disease caused by the pathogen as a function of the fold change resistance of the pathogen infecting the patients;

d) comparing, by the computer apparatus, the fold change resistance value of the pathogen infecting the patient to the clinical cut-off value;

e) calculating, by the computer apparatus, the predicted treatment response of a disease caused by the pathogen, and

f) outputting the results of the computer-generated estimate of the treatment response.

2.   (Withdrawn) A method according to claim 1, wherein the cut-off value is determined as a function of treatment response data in treated subjects, considering baseline pathogen load, baseline fold change resistance and baseline activity of coadministered drugs targeted to the pathogen.

3.   (Original) A method according to claim 1, wherein the cut-off value is calculated by reference to the pathogen load drop.

4.   (Original) A method according to claim 3, wherein the cut-off value is calculated by

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reference to the log pathogen load drop.

5.   (Withdrawn) A method according to claim 4, wherein the log pathogen load drop is

calculated by performing a linear regression analysis using data from a dataset of treatment

response data, wherein the log pathogen load drop *LogPL drop$_i$,* for the pathogen infecting a

patient *i,* is modelled as the sum of all of the individual contributions for factors that influence

pathogen load drop, according to the following equation:

$$LogPLdrop_i = \beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(PSS_i) + \beta_3(1/FC_i) + \varepsilon_i$$

wherein *BaselinePL$_i$* represents the pathogen load of the patient measured at the start

of treatment by the drug,

PSS$_i$ is a phenotypic sensitivity score representing the number of active drugs in the

background treatment regimen for the patient, excluding the drug whose contribution to

treatment response is being modelled,

FC$_i$ is a baseline fold change resistance,

β_0 is the intercept,

β_1 is a coefficient representing the increase in log pathogen load drop per unit

increase of the log of the *BaselinePL$_i$,*

β_2 is a coefficient indicating the increase in log pathogen load drop per unit increase

of the number of sensitive drugs in the background treatment regimen,

β_3 is a coefficient indicating the increase in log pathogen load drop per unit increase

of the inverse of *FC$_i$,*

and wherein the error term, *ε_i,* represents the difference between the modelled prediction

and the experimentally determined measurement.

6.   (Original) A method according to claim 4, wherein the log pathogen load drop is

calculated by performing a linear regression analysis using data from a dataset of treatment

response data, wherein the log pathogen load drop *LogPL drop$_i$,* for the pathogen infecting a

patient *i,* is modelled as the sum of all of the individual contributions for factors that influence

pathogen load drop, according to the following equation:

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$$LogPLdrop_i = \beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(cPSS_i) + \beta_3(cPSS_i)^2 + \beta_4(FC_i)^p + \beta_5(H_5) + ... + \beta_n(H_n) + \varepsilon_i$$

wherein the terms of the equation are the same as those given in claim 5, and additionally, p is a power transformation (e.g. ranging from -3 to 1) and H_5 to H_n are treatment history parameters or parameters describing the background therapy as a function of a certain therapeutic class.

7.　　(Withdrawn) A method according to claim 1, wherein the cut-off response value is calculated by reference to the probability of the pathogen being susceptible to treatment by the drug for the patient, herein termed *Prob of success*.

8.　　(Withdrawn) A method according to claim 7, wherein *Prob of success* is calculated by performing a logistic regression analysis using data from a dataset of treatment response data, wherein *Prob of success* is modelled according to the following equation:

$$Prob \ of \ success = \frac{\exp(\beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(PSS_i) + \beta_3(1/FC_i))}{(1 + \exp(\beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(PSS_i) + \beta_3(1/FC_i)))}$$

wherein *BaselinePL_i* represents the pathogen load of the patient measured at the start of treatment by the drug,

PSS_i is a phenotypic sensitivity score representing the number of active drugs in the background treatment regimen for the patient, excluding the drug whose contribution to treatment response is being modelled,

FC_i is a baseline fold change resistance,

β_0 is the intercept,

β_1 is a coefficient representing the increase in log pathogen load drop per unit increase of the log of the *BaselinePL_i*,

β_2 is a coefficient indicating the increase in log pathogen load drop per unit increase of the number of sensitive drugs in the background treatment regimen, and

β_3 is a coefficient indicating the increase in log pathogen load drop per unit increase of the inverse of *FC_i*.

9.　　(Original) A method according to claim 1, wherein the cut-off fold change resistance value is calculated by reference to the likelihood of a patient achieving treatment success or

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failure, where a definition of success is having an undetectable pathogen load after treatment
with a particular drug, using a classification tree.

10.   (Previously Presented) A method according to claim 9, wherein the clinical cut-off value
is defined as the fold change resistance threshold value that makes the best distinction between
the population with successful treatments and the population with unsuccessful treatments.

11.   (Original) A method according to anyone of the preceding claims, wherein the baseline
fold change resistance is determined by comparing the genotype of the disease causing pathogen
to phenotype data collected from a group of patients infected with a pathogen of similar
genotype.

12.   (Currently Amended) A method according to claim 11, wherein the baseline fold change
resistance is determined using the Virtual Phenotype system, or a variation thereof by predicting
the drug resistance phenotype of a pathogen genotype.

13.   (Previously Presented) A method according to claim 1, that incorporates two or more of
the methods of calculating the cut-off value by
    i) reference to the log pathogen load drop wherein the log pathogen load drop is calculated
    by:
        a) performing a linear regression analysis using data from a dataset of treatment response
        data, wherein the log pathogen load drop $LogPL\ drop_i$, for the pathogen infecting a
        patient i, is modelled as the sum of all of the individual contributions for factors that
        influence pathogen load drop, according to the following equation:

$$LogPLdrop_i = \beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(PSS_i) + \beta_3(1/FC_i) + \varepsilon_i$$

        wherein $BaselinePL_i$ represents the pathogen load of the patient measured at
        the start of treatment by the drug,
            PSS_i is a phenotypic sensitivity score representing the number of active drugs
        in the background treatment regimen for the patient, excluding the drug whose
        contribution to treatment response is being modelled,

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FC_i is a baseline fold change resistance,

β_0 is the intercept,

β_1 is a coefficient representing the increase in log pathogen load drop per unit increase of the log of the $BaselinePL_i$,

β_2 is a coefficient indicating the increase in log pathogen load drop per unit increase of the number of sensitive drugs in the background treatment regimen,

β_3 is a coefficient indicating the increase in log pathogen load drop per unit increase of the inverse of FC_i,

and wherein the error term, ε_i, represents the difference between the modelled prediction and the experimentally determined measurement, or

b) performing a linear regression analysis using data from a dataset of treatment response data, wherein the log pathogen load drop $LogPL\ drop_i$, for the pathogen infecting a patient i, is modelled as the sum of all of the individual contributions for factors that influence pathogen load drop, according to the following equation:

$$LogPLdrop_i = \beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(cPSS_i) + \beta_3(cPSS_i)^2 + \beta_4(FC_i)^p + \beta_5(H_5) + \ldots + \beta_n(H_n) + \varepsilon_i$$

wherein p is a power transformation (e.g. ranging from -3 to 1), and

H_5 to H_n are treatment history parameters or parameters describing the background therapy as a function of a certain therapeutic class;

or

ii) reference to the probability of the pathogen being susceptible to treatment by the drug for the patient, herein termed *Prob of success* wherein *Prob of success* is calculated by performing a logistic regression analysis using data from a dataset of treatment response data, wherein *Prob of success* is modelled according to the following equation:

$$Prob\ of\ success = \frac{\exp(\beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(PSS_i) + \beta_3(1/FC_i))}{(1 + \exp(\beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(PSS_i) + \beta_3(1/FC_i)))};$$

and calculating the cut-off fold change resistance value by reference to the likelihood of a patient achieving treatment success or failure, where a definition of success is having an undetectable pathogen load after treatment with a particular drug, using a classification tree.

14. - 15.   (Cancelled).

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16.   (Previously Presented) A method according to claim 1, wherein the disease causing

pathogen is obtained from a patient sample chosen from a blood sample, a biopsy sample, a

plasma sample, a saliva sample, a tissue sample, and a bodily fluid or mucous sample.

17.   (Previously Presented) A method according to claim 1, wherein the disease causing

pathogen is a virus.

18.   (Original) A method according to claim 17, wherein the disease causing virus is chosen

from HIV, HCV and HBV.

19.   (Previously Presented) A method according to claim 1, wherein the method is performed

for a number of candidate drugs so as to provide information on the predicted fold resistance

exhibited by the pathogen to a spectrum of candidate drugs.

20.   (Previously Presented) A diagnostic method for optimising a drug therapy in a patient,

comprising performing a method according to claim 1 for each drug or combination of drugs

being considered to obtain a series of drug resistance phenotypes and therefore assess the effect

of the plurality of drugs or drug combinations on the pathogen with which the patient is infected

and selecting the drug or drug combination for which the pathogen is predicted to have the

lowest fold resistance.

21.   (Currently Amended) A method according to claim 1 ~~for~~ further comprising assessing

the efficiency of ~~a~~ the patient's therapy, ~~or for~~ evaluating a therapy or optimizing a therapy.

22.   (Currently Amended) A computer-based diagnostic system for predicting clinical

response to a drug of a disease causing pathogen comprising: a) means for obtaining a genetic

sequence of the disease producing pathogen; b) means for identifying at least one mutation in the

genetic sequence of the disease producing pathogen; c) genotype database means comprising

genotype entries; d) phenotype database means comprising phenotypes of patient fold change

response values; e) clinical response database means comprising clinical response to drug

treatment for reference sample patients; f) correlation means correlating a genotype entry with a

phenotype, where the genotype entry corresponds with the obtained genetic sequence of the disease producing pathogen; g) means for modelling clinical response to a drug of the disease causing pathogen by determining whether the patient fold change response is above a cut-off value, wherein the cut-off value is determined using the clinical response database means and comprises the fold change response value at which a clinically relevant diminished clinical response is observed; and h) means for predicting the clinical response to a drug of a disease by determining whether the patient fold change response is above the cut-off value; and i) means for generating an output of the predicted clinical response to a drug of a disease causing pathogen.

23.   (Withdrawn) A diagnostic system according to claim 22, wherein the cut-off value is determined as a function of treatment response data in treated subjects, considering baseline pathogen load, baseline fold change resistance, baseline activity of co-administered drugs targeted to the pathogen and treatment history.

24. - 25.   (Cancelled).

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